UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/500,173 | 06/24/2004 | Katsuhito Takahashi | 4439-4022 | 3299 |

27123 7590 12/10/2008

MORGAN & FINNEGAN, L.L.P.
3 WORLD FINANCIAL CENTER
NEW YORK, NY 10281-2101

| EXAMINER | |
|---|---|
| POPA, ILEANA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 12/10/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOPatentCommunications@Morganfinnegan.com
Shopkins@Morganfinnegan.com
jmedina@Morganfinnegan.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/500,173 | TAKAHASHI ET AL. | |
| | Examiner | Art Unit | |
| | ILEANA POPA | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,6,7,20,21,23-26,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,20,21,23-26,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Claims 2-5, 8-19, 22, and 27-34 have been cancelled. Claims 1 and 35 have been amended.

Claims 1, 6, 7, 20, 21, 23-26, 35, and 36 are pending and under examination.

***Specification***

2. The disclosure is objected to because of the following informalities: improper English translation and arrangement (see the non-final Office action of 04/21/2006). However, upon Applicants request filed on 07/21/2006, the submission of a re-translated version of the specification is deferred.

***Response to Arguments***

***Claim Objections***

3. The objection to claim 1 is withdrawn in response to Applicant's amendment to the claim filed on 09/03/2008.

***Double Patenting***

4. The provisional double patenting rejection of claims 1, 6, and 7 are provisionally as being unpatentable over claims 1 and 7 of copending Application No. 10/477,797 in view of both Martuza (U.S. Patent No. 5,728,379, of record) and Wagstaff et al. (Gene

Therapy, 1998, 5: 1566-1570) is withdrawn because claims 1 and 7 of the copending Application No. 10/477,797 have been cancelled.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 6, 7, 20, 21, 25, 35, and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 5,728,379, of record), in view of each Chung et al. (J Virol, 1999, 73: 7556-7564, of record), Yamamura et al. (Cancer Res 5/2001, 61: 3969-3977, of record), Wagstaff et al., and Foster et al. (J Virol Methods, 1998, 75: 151-160).

Martuza et al. teach an HSV vector comprising a DNA fragment comprising tissue-specific promoters, the ICP4 gene downstream to the tissue-specific promoter, *lacZ* upstream to the tissue-specific promoters derived from genes highly expressed in tumor cells, and tissue-specific enhancers upstream to the tissue-specific promoters, wherein the vector is obtained by inserting the DNA fragment into the HSV genome and wherein the vector expresses therapeutic factors in a tissue-specific manner; the DNA fragment could be inserted into the *tk* locus or into a locus other than the *tk* locus, wherein the vector with intact *tk* is sensitive to ganciclovir (claims 1 and 6) (column 4, lines 40-59, Figure 1 and its Brief description at column 6, lines 42-45, column 4, lines

30-67, column 11, lines 4-16, column 25, lines 39-56, claims 1-3, 12, and 13). Therefore, Martuza et al. also teach a method for expression of a therapeutic factor in tumor cells by using an HSV vector, wherein the HSV vector does not replicate in normal cells (claims 20 and 25). In addition to the above, Martuza et al. teach the use of ganciclovir to suppress the replication of their HSV vector, i.e., they teach a method for suppressing the expression of the gene encoding the therapeutic factor (claim 21) (column 7, lines 20-35, column 25, lines 51-55, column 33, lines 48-64). Martuza et al. teach their HSV vector as comprising a disrupted ribonucleotide reductase gene, wherein disruption takes place via *lacZ* insertion into the ribonucleotide reductase gene locus by homologous recombination, i.e., co-transfecting the *lacZ*-containing fragment with a viral DNA into Vero cells (i.e., cells which do not express ICP4 and which contain transcription factors that activate the calponin promoter, see Example A of the instant specification), and purifying clones by limiting dilution (claims 1, 35, and 36) (Fig. 4 and 5, column 5, lines 1-9 and 39-45, column 21, lines 40-60, Example 1). Martuza et al. teach that ribonucleotide reductase gene disruption is essential for therapeutic vectors, wherein disruption results in increased sensitivity to acyclovir and ganciclovir and wherein the ribonucleotide reductase-disrupted vectors are less likely to replicate in normal cells (column 22, lines 1-3 and 24-40, column 25, lines 57-62).

Although Martuza et al. teach that the DNA fragment comprising ICP4 operably linked the tissue specific promoter can be inserted by homologous recombination in any location of the HSV genome, they do not specifically teach inserting into the ribonucleotide reductase locus (claims 1 and 35). However, inserting DNA constructs

into the ribonucleotide reductase locus to obtain therapeutic HSV vectors is taught by the prior art. For instance, Chung et al. teach insertion of a DNA comprising a tissue specific promoter operably linked to a gene essential for HSV virulence into the ribonucleotide reductase locus (p. 7558, Fig. 1, p. 7557, column 1, second paragraph and column 2, *Results*). Based on these teachings and on the teachings of Martuza et al. that the DNA fragment can be inserted at any locus in the HSV genome, it would have been obvious to one of skill in the art, at the time the invention was made, to insert the DNA fragment comprising ICP4 gene operably linked the tissue specific promoter into the ribonucleotide reductase locus, to achieve the predictable result of obtaining a vector suitable for gene therapy, which vector does not replicate in the normal cells and which vector exhibits increased sensitivity to acyclovir and ganciclovir. With respect to the limitation of cloning without agarose overlay (claim 35) it is noted that the patentability of the composition does not depend on the method of obtaining it (see MPEP 2113 [R-1]). The instant end product (i.e., the HSV vector) is identical to the end product taught by the combined teachings above, regardless of whether cloning takes place with or without agarose overlay. Applicant did not provide any evidence that cloning in the absence of agarose overlay results in an HSV vector which is structurally different from the HSV vector taught by the cited prior art.

Although Martuza et al. and Chung et al. teach a cell-specific promoter and an enhancer, they do not specifically teach the full length calponin promoter or the 4F2 enhancer (claims 1 and 7). Yamamura et al. teach the calponin promoter driving the expression of the ICP4 gene and the 4F2 enhancer, wherein the 4F2 enhancer is

integrated upstream to the calponin promoter and wherein the 4F2 enhancer further upregulates ICP4 expression (p. 3970, column 1, fourth full paragraph and Figure 1A and 1B, p. 3972, column 1, first paragraph). Yamamura et al. also teach that calponin is highly expressed in a variety of human soft tissue and bone tumors (Abstract, p. 3969, column 2, p. 3976, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the HSV vector of Martuza et al. by using the calponin promoter together with the 4F2 enhancer, with a reasonable expectation of success. One of skill in the art would have been motivated to use the calponin promoter in order to target therapeutics to the human soft and bone tumor cells. One of skill in the art would have been motivated to use the 4F2 enhancer because Yamamura et al. teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the calponin promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a vector because the art teaches that such vectors can be successfully made and because Martuza et al. teach that promoters derived from genes highly expressed in tumor cells can be successfully used to specifically drive vector replication in tumor cells.

Martuza et al., Chung et al., and Yamamura et al. do not teach inserting the EGFP gene downstream to the ICP4 gene via IRES (claims 1 and 35). However, at the time the invention was made, the use of IRES to obtain bicistronic HSV vectors expressing GFP as a reporter to identify the transduced cells was taught by the prior art (see Wagstaff et al., Abstract, p. 1567, Fig. 1). It would have been obvious to one of

skill in the art, at the time the invention was made, to modify the application claims by inserting GFP downstream to ICP4 via IRES to achieve the predictable result of identifying the transduced cells. While Wagstaff et al. teach GFP and not EGFP, it is noted that EGFP was known and used in the prior art (see Foster et al., Abstract). Therefore, one of skill in the art would have known to substitute GFP with EGFP to achieve the predictable result of identifying transduced cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that the Examiner's reliance on Martuza's statement that the DNA fragment could potentially be inserted in other locations besides the *tk* locus to preserve the vector's sensitivity to ganciclovir is misplaced because it is well beyond the level of one skilled in the art at the time of filing to place the DNA fragment anywhere else. Applicant argues that it is well recognized that such statements as the one made by Martuza do not constitute the teaching of prior art because they are overly broad, and in case of gene manipulation unpredictable and requiring undue experimentation.

Applicant notes that the Examiner admits that Martuza does not teach inserting a DNA fragment comprising ICP4 operably linked to the tissue specific promoter into the ribonucleotide reductase locus by homologous recombination; however, according to the Examiner, this it would be obvious in view of Chung. Applicant submits that, even if one of skill in the art would combine Chung with Martuza, it is still not clear how the

claimed construct could be obtained without employing impermissible hindsight. For instance, Applicant argues, Chung discloses a homologous recombination of a B-myb promoter- γ34.5 gene construct into the ICP6 locus, where the ICP6 locus prior to recombination contains a *lacZ* insert. Applicant argues that Chung does not describe how to insert other tissue-specific promoters (e.g., the albumin promoter of Martuza), in conjunction with the ICP4 gene and *LacZ* into the ICP6 locus. Furthermore, Applicant argues, recombination with the *LacZ* insert is an essential part of the Chung disclosure and cannot be ignored. In fact, Chung utilizes the removal of the *LacZ* gene (lack of β-galactosidase expression) from the RR locus as a marker to identify whether or not recombination has occurred. Applicant submits that Martuza discloses an HSV vector which has a tissue specific promoter (albumin), ICP4 gene and *LacZ* inserted in a thymidine kinase (tk) locus. Martuza utilizes β-galactosidase expression (*LacZ*) as an indicator of transformation. Therefore, Applicant argues, if the homologous recombination technique of Chung, i.e., recombination of a desired insert with the *LacZ* of the ICP6 locus (i. e., MGH1; page 7557 of Chung), was employed with the construct of Martuza (i.e., a tissue specific promoter (albumin), ICP4 gene and LacZ) one skilled in the art would have no reasonable expectation of success because the construct would not be distinguishable from the background cells.

Applicant argues that making a construct would require great deal of undue experimentation, beyond what is taught in Martuza and Chung. Thus, even in combination, the cited art would not produce the claimed HSV vector that has a full length promoter of the human calponin gene, the ICP4 gene, and two marker genes -

the *LacZ* (marker) gene and the EGFP (marker) gene inserted in the ribonucleotide reductase (RR) gene locus.

In addition to the arguments presented above, Applicant directs the Examiner's attention to secondary considerations such as long-felt but unsolved needs and failure of others. For instance, Applicant argues, while Martuza recognizes that a construct inserted into the ribonucleotide reductase (RR) gene locus and a deletion to inactivate the $\gamma$34.5 gene are essential for therapeutic vectors because of the increase in acyclovir and ganciclovir sensitivity and reduced possibility of replication in normal cells, Martuza only teaches an HSV vector with DNA construct that has a tissue specific promoter, ICP4 gene and *lacZ* inserted in a thymidine kinase (*tk*) locus, which results in an inactive *tk* gene. In fact, Applicant argues that Martuza did not succeed in producing a cell-specific expression replication vector where a DNA fragment coupling ICP4, albumin promoter and *lacZ* is inserted into the ribonucleotide reductase (ICP6) gene locus by homologous recombination, i.e., long-felt but unsolved needs. Martuza was only able to produce the HSV vector comprising the ICP4 gene which is linked to a cell-specific promoter inserted into the ribonucleotide reductase locus for the first time in 2006 as evidenced by Kuroda, et al. (BMC Biotechnology, 2006, 6:40) well after the applicants' 2002 filing demonstrating failure of others to make the claimed construct prior to the Applicant's invention. Moreover, Applicant argues, Martuza used a modified method of producing genetic recombinants termed "bacterial artificial chromosome (BAC) -based system" which was only developed by Y. Saeki et al. in 2003 (Methods Mol. Med. 2003 ;76:51-60). Applicant asserts that while the prior art points to the

desirability of the clamed system, nowhere in the prior art was the claimed system ever produced. In view of the arguments presented above and other secondary considerations, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues that Martuza's teaching of a fragment being inserted in other locations besides the *tk* locus does not constitute the teaching of prior art because such a teaching is overly broad. In response to this argument, it is note that MPEP 2123 [R-5] states:

> I. PATENTS ARE RELEVANT AS PRIOR ART FOR ALL THEY CONTAIN
>
> The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).
>
> A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S.

> 975 (1989). See also > Upsher-Smith Labs. v. Pamlab, LLC, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005) (reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component);< Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").

Therefore, Applicant's argument is not found persuasive. Martuza's teaching of inserting fragments into different locations is considered a teaching of the prior art. The argument that gene manipulation is unpredictable and requires undue experimentation is just an argument not supported by any evidence. In fact, the prior art teaches using nothing but routine experimentation to construct viral vectors with insertions at diverse locations.

With respect to the combination of Chung with Martuza, Applicant argues that the references are not combinable because Martuza utilizes the *LacZ* gene as an indicator of transformation, whereas Chung utilizes the removal of the *LacZ* gene from RR locus as a marker or index. Therefore, Applicant argues, if the homologous recombination technique of Chung, was employed with the construct of Martuza one skilled in the art would have no reasonable expectation of success because the construct would not be distinguishable from the background cells. This argument is not found persuasive. Chung teaches using homologous recombination to obtain a vector wherein the ribonucleotide reductase locus is disrupted by *lacZ* insertion; this vector is further used to obtain a second vector wherein *lacZ* is replaced with a construct comprising a tissue specific promoter operably linked to a gene essential for HSV virulence, wherein replacement takes place via homologous recombination (p. 7557,

column 1 and 2; p. 7558, Fig. 1). Therefore, Chung teaches the routine use of homologous recombination to insert different construct into the ribonucleotide reductase locus. By modifying Martuza according to Chung's teachings, one of skill in the art would have introduced Martuza's DNA fragment (i.e., comprising a tissue-specific promoter, the ICP4 gene downstream to the tissue-specific promoter, and *lacZ* upstream to the tissue-specific promoter) into the ribonucleotide reductase locus, leaving the *tk* locus intact. One of skill in the art would have been capable to select the recombinants based on sensitivity to ganciclovir.

Applicant argues that making a construct would require great deal of undue experimentation, beyond what is taught in Martuza and Chung. This argument is not found persuasive because obtaining such constructs was routine in the prior art, as demonstrated by Chung.

Applicant also argues that Chung does not describe how to insert other tissue-specific promoters in conjunction with the ICP4 gene and *LacZ* into the ICP6 locus. This argument is not found persuasive because is just an argument not provided by any evidence. Operably linking genes to different promoters and insert them into vectors at different location was routine in the art. One of skill in the art would have known to use routine experimentation. The fact is that Chung et al. teach recombination at the RR locus and the nature of the DNA fragment to be inserted is irrelevant; any fragment can be inserted by following Chung's teachings. Applicant did not provide any evidence to the contrary.

Applicant also argues long-felt but unsolved needs. This argument is not found persuasive because such construct with DNA fragments inserted into the ribonucleotide reductase gene locus such as to deletion and inactivate the γ34.5 gene were taught by Chung before the instant invention was made (see the rejection above).

Applicant also argues failure of others, i.e., that Martuza was only able to produce the HSV vector comprising the ICP4 gene which is linked to a cell-specific promoter inserted into the ribonucleotide reductase locus for the first time in 2006 as evidenced by Kuroda, et al. well after the filing date of the instant application. This argument is not found persuasive because inserting a gene operably linked to a cell-specific promoter into the ribonucleotide reductase locus was already taught by Chung. The fact that Chung's gene is not ICP4 is irrelevant since, as noted above, any gene can be inserted by following Chung's teachings.

For the reasons set forth above, the rejection is maintained.

7. Claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with each Chung et al., Yamamura et al., Wagstaff et al., and Foster et al., in further view of Miyatake et al. (Stroke, 1999, 30: 2431-2439).

The teachings of Martuza et al., Chung et al., Yamamura et al., Wagstaff et al., and Foster et al. are applied as above for claims 1, 6, 7, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., and Chung et al. do not teach therapy by targeting the virus to proliferating smooth muscle cells (claim 26). However, at the time the invention

was made, therapy by specific targeting proliferating smooth muscle cells was taught by the prior art. For example, the prior art teaches using tissue specific replication competent HSV vectors to inhibit smooth muscle cell proliferation (see Miyatake et al., the whole paper). One of skill in the art would have known, would have been motivated, and would have been expected to have a reasonable expectation of success in using the vector taught by Martuza et al., Yamamura et al., and Chung et al. (i.e., replication competent and, since calponin is highly expressed in proliferating smooth muscle cells, specific for proliferating smooth muscle cells) to treat disorders associated with smooth muscle cell proliferation, because the art teaches the usefulness of using such vectors to treat disorders associated with cell proliferation, including those characterized by smooth muscle proliferation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that the addition of Miyatake does not remedy the deficiencies noted above. Applicant's argument is acknowledged however, the rejection is maintained for the reasons set forth above.

8. Claims 1, 6, 7, 20, 21, 23-25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with each Chung et al., Yamamura et al., Wagstaff et al., and Foster et al., in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341).

The teachings of Martuza et al., Yamamura et al., and Chung et al. are applied as above for claims 1, 6, 7, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., and Chung et al. do not teach detecting the *in vivo* distribution of the vector by determining tk activity using positron emission tomography (PET) and FIAU labeled with $^{124}$I (claims 23 and 24). Tjuvajev et al. teach the noninvasive imaging of *tk* gene transfer and expression by PET and FIAU labeled with $^{124}$I. It would have been obvious, to one of skill in the art, at the time the invention was made, to monitor the distribution and expression of the vector taught by Martuza et al., Yamamura et al., and Chung et al. by using PET and FIAU labeled with $^{124}$I, with a reasonable expectation of success. The motivation to do so is provided by Tjuvajev et al., who teach their method as useful for providing the information necessary for monitoring clinical gene therapy. One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of the method to monitor transgene expression.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Tjuvajev et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons set forth above.

***Conclusion***

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Examiner, Art Unit 1633